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Short communication

Efficacy of primary series AZD1222 (ChAdOx1 nCoV-19) vaccination against SARS-CoV-2 variants of concern: Final analysis of a randomized, placebo-controlled, phase 1b/2 study in South African adults (COV005)

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ABSTRACT

COVID-19 vaccine efficacy (VE) has been observed to vary against antigenically distinct SARS-CoV-2 variants of concern (VoC). Here we report the final analysis of VE and safety from COV005: a phase 1b/2, multicenter, double-blind, randomized, placebo-controlled study of primary series AZD1222 (ChAdOx1 nCoV-19) vaccination in South African adults aged 18–65 years. South Africa's first, second, and third

Abbreviations: AE, Adverse event; BMI, Body mass index; CI, Confidence interval; Ct, Cycle threshold; FU, Follow-up; HIV, Human immunodeficiency virus; IQR, Interquartile range; NA, Not applicable; NAAT, Nucleic acid amplification test; NEC, Not elsewhere classified; PCR, Polymerase chain reaction; SAE, Serious adverse event; SD, Standard deviation; VE, Vaccine efficacy; VoC, Variants of concern; WT, Wild type.

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waves of SARS-CoV-2 infections were respectively driven by the ancestral SARS-CoV-2 virus (wild type, WT), and SARS-CoV-2 Beta and Delta VoCs. VE against asymptomatic and symptomatic infection was 90.6% for WT, 6.7% for Beta and 77.1% for Delta. No cases of severe COVID-19 were documented ahead of unblinding. Safety was consistent with the interim analysis, with no new safety concerns identified. Notably, South Africa's Delta wave occurred ≥ 9 months after primary series vaccination, suggesting that primary series AZD1222 vaccination offers a good durability of protection, potentially due to an anamnestic response.

Clinical trial identifier: CT.gov NCT04444674.

1. Introduction

Coronavirus Disease 2019 (COVID-19) vaccines have been rapidly developed and approved for licensure over the past two years. The emergence of new variants of concern (VoCs) containing mutations that affect transmissibility or confer the ability to evade vaccine- and infection-induced antibodies requires analysis of vaccine efficacy (VE) against specific SARS-CoV-2 variants.

South Africa experienced an ancestral SARS-CoV-2 (wild type, WT) wave in March 2020, which peaked in July 2020 [1]. The Beta (B.1.351) variant, which possessed relative neutralization resistance to antibodies induced by ancestral virus infection and most first-generation COVID-19 vaccines, fueled a second wave of infections from November 2020, peaking in January 2021. This was followed by a third wave from July–September 2021 driven by infections caused by the Delta variant [2], which was two-fold more transmissible than the ancestral virus.

An interim analysis using data from four AZD1222 (ChAdOx1 nCoV-19) studies conducted in Brazil, South Africa and the UK between April 23, 2020–November 4, 2020, reported an overall VE for symptomatic infection of 66.7% (95% confidence interval [CI] 57.4, 74.0) [3]. VE at preventing symptomatic infection with the Alpha (B.1.1.7) variant in the UK was 74.6% (95% CI 41.6, 88.9) [4]. Primary analysis of the pivotal phase 3 trial of AZD1222 demonstrated a VE of 74.0% (95% CI 65.3, 80.5) at preventing symptomatic COVID-19 with predominantly the ancestral virus in the United States, Chile, and Peru (data cut-off: March 5, 2021) [5].

Previously, we reported an overall VE for two-dose primary series AZD1222 vaccination of 21.9% (95% CI −49.9, 59.8) against mild-to-moderate COVID-19 in SARS-CoV-2-naïve South African participants (data-cut off: January 15, 2021) [6]. The majority of these cases were driven by the Beta variant with a VE of 10.4% (95% CI −76.8, 54.8) against mild-to-moderate COVID-19 observed in a secondary analysis [6]. In this brief report, we report our final analysis for overall and variant-specific VE and safety of primary series AZD1222 from a multicenter phase 1b/2 trial in South Africa.

2. Methods

2.1. Trial design

COV005 is a phase 1b/2 double-blind, randomized, placebo-controlled study (NCT04444674; PACTR202006922165132) assessing the safety and efficacy of AZD1222 in South African adults. Our study protocol detailing participant eligibility, sample size determination etc. has been published [6]. Healthy adults aged 18–65 years were recruited between June 24, 2020–November 9, 2020 and randomized (1:1) to receive two doses of placebo (saline) or AZD1222. This is the final VE analysis through to the time of unblinding of participants.

2.2. Endpoints

The primary endpoint was VE in the context of polymerase chain reaction (PCR)-positive symptomatic COVID-19 occurring > 14 days after the second dose of study drug, and safety. Secondary objectives included VE based on SARS-CoV-2 variant, and reactogenicity.

2.3. SARS-CoV-19 nucleic acid amplification test (NAAT) testing

NAAT testing was performed at the Vaccines and Infectious Diseases Analytics Research Unit (VIDA, Johannesburg) or the University of Cape Town Lung Institute (Cape Town, South Africa). Nasopharyngeal swabs were tested using Emergency Use Authorization SARS-CoV-2 assays which target two regions within the nucleocapsid gene (N1 and N2) and a third assay which detects the human RNase P gene [7,8]. Results were classified as positive for SARS-CoV-2 when both the N1 and N2 targets were detected at a cycle threshold (Ct) < 40 and classified as inconclusive if only N1 or N2 was detected with Ct values < 40. If a repeat swab test tested inconclusive, the participant was considered to be infected with SARS-CoV-2. In order for negative results to be valid, the human RNase P assay needed to be detected with a Ct < 40.

2.4. Whole genome sequencing

Whole genome sequencing of samples was done either at VIDA or the KwaZulu-Natal Research Innovation and Sequencing Platform (KRISP). Superscript IV with random hexamers (Life Technologies, Carlsbad, CA) were used to generate cDNA from SARS-CoV-2 NAAT confirmed nasopharyngeal samples. The QIAseq DIRECT SARS-CoV-2 Primer Panel (QIAGEN, Germany) or the ARCTIC V3 protocol [9–11] and Illumina® Nextera Flex DNA Library Prep kits were used to amplify, and index paired end libraries of genomic DNA according to manufacturers' instructions [12]. These libraries were sequenced on a 500 cycle v2 MiSeq Reagent Kit on an Illumina MiSeq instrument (Illumina, San Diego, CA, USA).

2.5. Genome assembly and phylogenetic analysis

Genome Detective 1.126 (https://www.genomedetective.com) and the Coronavirus Typing Tool were used to generate paired-end fastq reads [13]. Low-quality mutations were filtered out of the initial assembly generated from Genome Detective using bcftools 1.7–2 mpileup method. The whole genomes were compared against the global reference dataset using a custom pipeline based on a local version of NextStrain for variant classification of sequenced isolates. The pipeline contains several python scripts that manage the analysis workflow. It performs alignment of genotypes in Nextalign (https://github.com/neherlab/nextalign), phylogenetic tree inference in IQ-Tree, tree dating [14] and ancestral

state construction and annotation (https://github.com/nextstrain/ncov).

2.6. Statistical methods

For this report, incidence of COVID-19 disease was calculated as the number of participants with COVID-19 divided by the total in person follow-up time in days. Participants were followed from two weeks post-second dose until the first of the following events: withdrawal, death, SARS-CoV-2 infection, unblinding or censored by 15 November 2021. VE was calculated as 1 minus the relative risk (incidence in vaccinated individuals divided by incidence in placebo recipients) and 95% CI were calculated using the Clopper-Pearson exact methods. Participants were grouped by treatment received, regardless of their planned group assignment. Only participants who received two doses of placebo or vaccine and had sufficient follow-up were included in the analysis. VE was assessed against COVID-19 of any severity, and infection for WT, Beta and Delta variants. A sensitivity analysis was performed to include infections where the strain was unclassifiable. Infections pre-October 2020 were assigned WT classification, between October 2020 and April 2021 Beta classification, and between May and November 2021 Delta classification. Local and systemic Adverse events (AEs) were recorded for 28 days following each vaccination. Serious AEs (SAEs) were collected through the whole study period.

2.7. Ethics statement

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines. Participants were required to provide informed consent. The study was approved by the South African Health Products Regulatory Authority and institutional Ethics Committees.

3. Results

3.1. Study demographics and circulating variants

2130 healthy adults (including 104 living with HIV) aged 18–65 were randomized to receive two doses of placebo (1,065; 50%) or AZD1222 (1,065; 50%). A total of 960 (placebo) and 935 (vaccinated) participants were included in this analysis (Fig. 1). 107 (31 randomized to placebo and 76 randomized to AZD1222) participants did not receive two doses of the allocated treatment.126 participants were infected by SARS-CoV-2 < 14 days post-second dose (72 placebo and 54 AZD1222) and two placebo participants died < 14 days post-second dose. The median age of participants was 31 years, with most participants aged 18–45 (82.7%; Supplementary Table 1); 49.8% of participants were of normal weight and 42.6% were smokers. 7.5% of participants had either hypertension, diabetes or medical conditions related to the respiratory system (Supplementary Table 1).

The increased frequency of Beta, Delta and other VoCs temporally coincided with the peaks of infection in the study cohort (Fig. 2). The first wave of South African infections (June–August 2020) was dominated by the circulating WT, whereas the second (November 2020–March 2021) and third (May–August 2021) waves were mainly dominated by Beta and Delta variants, respectively.

3.2. Vaccine efficacy

For any infection, the mean time between second study injection and SARS-CoV-2 infection was 5.5 months in the placebo group and 4.5 months in vaccinees (Table 1); for the Delta variant, the mean time was 9.3 and 10.0 months, respectively. Follow-up time post second study injection was similar for mild and moderate cases.

When examining the effect on SARS-CoV-2 infection (i.e., inclusive of asymptomatic infection and cases not meeting criteria of severity), overall VE against SARS-CoV-2 infection was 38.3% (95% CI 15.1, 55.4; Table 1). VE against infection with WT was 90.6% (95% CI 35.4, 99.8) and 77.1% (95% CI 30.4, 94.4) against the Delta variant; whilst there was lack of VE against the Beta variant (6.7%; 95% CI −41.1, 38.5). Cumulative incidence over time for SARS-CoV-2 infection due to WT, Beta and Delta variants is shown in Fig. 3.

Overall VE against mild and moderate COVID-19 (no severe cases documented in the cohort before unblinding) for any variant was 45.2% (95% CI 19.7, 63.1; Supplementary Table 2). VE varied by

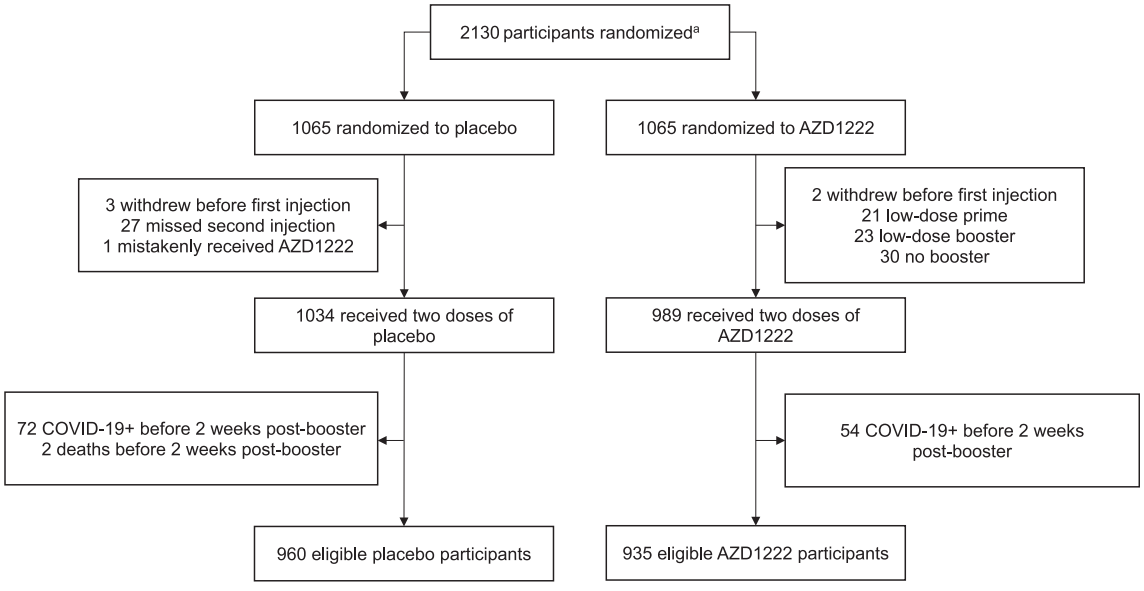

Fig. 1. Participant disposition. [a]Updated from enrollment reported in [6], to exclude five participants who were randomized but withdrew before they received their first injection.

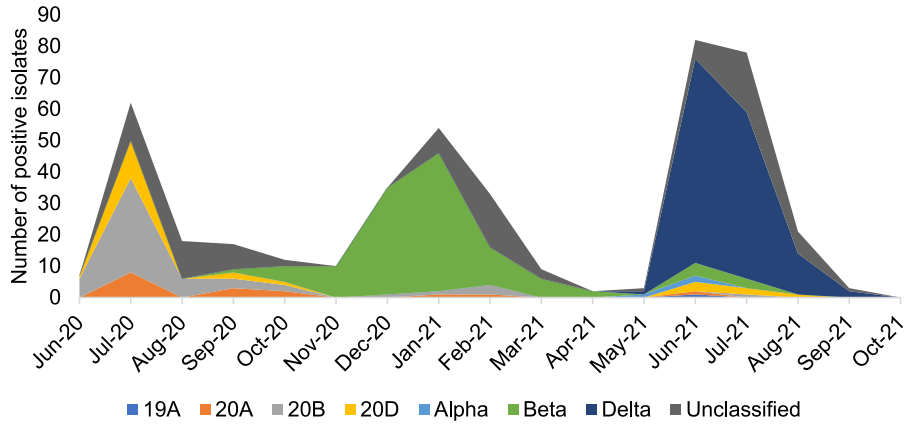

Fig. 2. Rolling mean number of total monthly SARS-CoV-2 infections through time. The color indicates the rolling mean of prevalence out of all samples for Alpha (light blue), Beta (green), Delta (dark blue) and unclassified (gray). The unclassified isolates were detected in individuals with viral loads too low (>32Ct) to get a definite strain classification. Abbreviation: Ct, Cycle threshold. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Vaccine efficacy.

Severity	SARS-CoV-2	Total cases	Placebo n = 960 Total FU time(days) = 244,140 Mean FU in days (SD) = 254 (71)			Vaccine n = 935 Total FU time (days) = 236,557 Mean FU in days (SD) = 253 (74)			VE (95% CI)
			n (%)	Mean FU, months (SD)	Incidence rate, person-days	n (%)	Mean FU, months (SD)	Incidence rate, person-days	
Any infection[a]	Any[b]	171	107 (11.1)	5.5 (2.7)	160	64 (6.8%)	4.5 (2.2)	98.7	38.3% (15.1, 55.4)
	WT	12	11 (1.1)	4.6 (3.1)	16.4	1 (0.1%)	0.6 (NA)	1.5	90.6% (35.4, 99.8)
	Beta	99	52 (5.4)	4.2 (1.7)	77.7	47 (5%)	4.0 (1.7)	72.5	6.7% (−41.1, 38.5)
	Delta	22	18 (1.9)	9.3 (1.0)	26.9	4 (0.4%)	10.0 (0.7)	6.2	77.1% (30.4, 94.4)
Mild/Moderate	Any[b]	124	81 (8.4)	5.6 (2.9)	121.1	43 (4.6%)	4.4 (2.6)	66.3	45.2% (19.7, 63.1)
	WT	10	9 (0.9)	4.6 (3.4)	13.5	1 (0.1%)	0.6 (NA)	1.5	88.5% (17.2, 99.7)
	Beta	70	37 (3.9)	4.1 (1.8)	55.3	33 (3.5%)	3.8 (1.9)	50.9	8% (−51.3, 44.2)
	Delta	21	17 (1.8)	9.4 (0.9)	25.4	4 (0.4%)	10 (0.7)	6.2	75.7% (25.6, 94.1)

[a] Includes symptomatic and asymptomatic infections.
[b] Includes infections from strains that were not classified as WT, Beta or Delta. Abbreviations: CI, Confidence interval; FU, Follow-up; NA, Not applicable; SD, Standard deviation; VE, Vaccine efficacy; WT, Wild type.

variant: 88.5% (95% CI 17.2, 99.7) against WT and 75.7% (95% CI 25.6, 94.1) against the Delta variant; VE against the Beta variant was 8% (95% CI −51.3, 44.2). Similar VE point-estimates were evident for only moderate COVID-19 although the CIs were wider. Distribution of infections by vaccination status, variant and severity are shown in Supplementary Table 2, and Supplementary Table 3 contextualizes the timing of sequences that were unclassified as part of this analysis. A sensitivity analysis showing the cumulative incidence for infection across variants, accounting for unclassified sequences, is shown in Supplementary Fig. 1.

3.3. Adverse events

AEs and SAEs are presented in Supplementary Tables 5 and 6, respectively. As previously reported [6], one vaccinee had severe Grade 3 fever which was considered related to AZD1222 by the investigator and was resolved within 48 h.

4. Discussion

Here, we present our final analysis of overall and variant-specific VE and safety of an AZD1222 primary series. We demonstrate high VE against WT SARS-CoV-2 infection, in line with previous findings [3,5]. VE against the Delta variant was also high, despite infections occurring 9–10 months after study participants had received their second dose of AZD1222. Given the timing of emergence of Delta, the lower VE we observed compared to WT may be due to waning of antibodies, viral escape from neutralizing antibodies induced by vaccination and increased transmissibility of this variant [15]. Despite this, VE observed against Delta across this timeframe points to good durability of protection, likely due to an anamnestic response from AZD1222. It is notable that no cases of severe disease were documented ahead of unblinding. Although the Delta variant wave was associated with the highest morbidity and mortality in South Africa, we did not identify any severe cases in our study during the Delta variant wave, probably due to individuals older than 65 years of age and those with uncontrolled chronic medical conditions not being eligible for study participation [16].

In contrast to WT and Delta variants, and in line with our previous interim analysis, VE against mild-moderate COVID-19 due to Beta variant was low, which was likely due to escape from vaccine-induced neutralizing antibody activity [6]. However, a subsequent real-world evidence study demonstrated an 83% risk reduction for hospitalization or death due to infection with the Beta or Gamma VoCs following AZD1222 vaccination, suggesting that cellular immunity may continue to provide protection against severe disease despite neutralizing antibody escape [17]. Despite the limited protection against symptomatic disease with Beta, vaccination campaigns that continued to deploy AZD1222 in line with

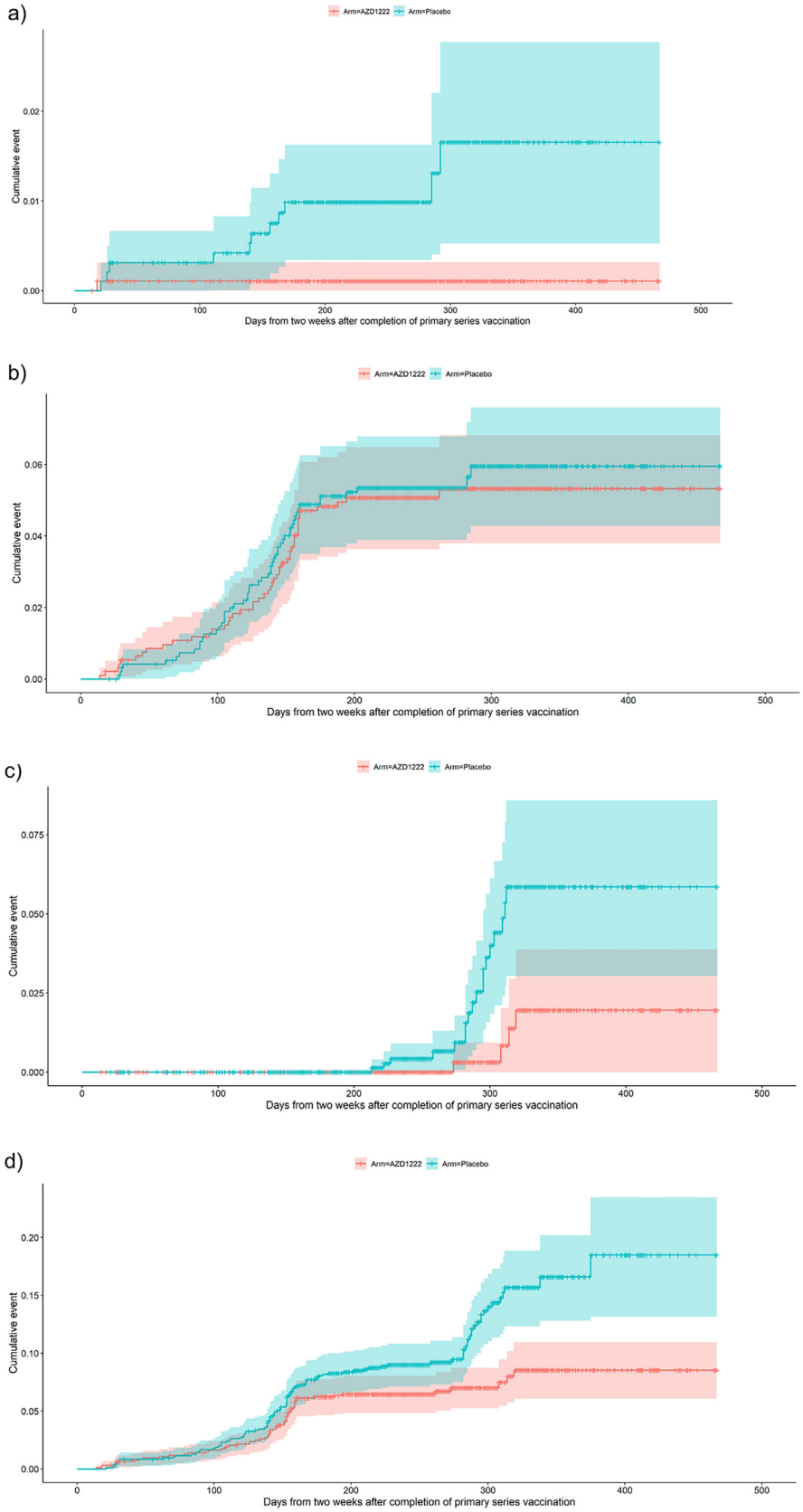

Fig. 3. Cumulative incidence over time for any SARS-CoV-2 infection (including both asymptomatic and symptomatic illness) due to wild type (a), Beta (b) and Delta (c) variants, and overall (d).

World Health Organization recommendations enabled the prevention of deaths in subsequent waves driven by Delta. The Delta variant wave in South Africa was the most severe in relation to deaths, contributing to 50% of the overall death toll which transpired from COVID-19 since the start of the pandemic until the end of the fourth wave, which was due to the Omicron variant [16]. Overall, this highlights that national immunization campaigns should not discontinue use of a vaccine based on experience with a single variant and only based on effectiveness against non-severe illness.

At the time of writing, the Omicron (B.1.1.529) VoC and sublineages thereof are the dominant variants across much of the world, with cases of a Delta Omicron (BA.1 × AY.4) recombinant variant also documented [18]. Third dose booster vaccination has been widely used as a mitigation strategy for breakthrough Omicron infection. However, due to preliminary immunogenicity studies favoring AZD1222–BNT162b2 or homologous BNT162b2 boosting strategies, booster doses of AZD1222 have largely been restricted to those unable to receive mRNA vaccines. Real-world data has shown similar vaccine effectiveness against symptomatic disease and hospitalization from Omicron with either an AZD1222 or BNT162b2 booster following AZD1222 primary series, indicating the potential wider utility of AZD1222 as a booster [19]. As our analysis was censored and participants unblinded before the emergence of Omicron, we await further studies to determine the VE of AZD1222 and other SARS-CoV-2 vaccines as primary series and boosters against Omicron and related subvariants.

5. Data sharing

Data are available at https://www.wits-vida.org; requests for data sharing should be directed to Professor Shabir A. Madhi, email: shabir.madhi@wits.ac.za.

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Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Shabir Madhi reports financial support was provided by GlaxoSmithKline. Shabir Madhi reports financial support was provided by AstraZeneca. Shabir Madhi reports financial support was provided by BMGF. Shabir Madhi reports financial support was provided by South African Medical Research Council. Shabir Madhi reports financial support was provided by Pfizer. Shabir Madhi reports financial support was provided by Minervax. Shabir Madhi reports financial support was provided by Novavax. Shabir Madhi reports financial support was provided by Providence. Shabir Madhi reports financial support was provided by Greenstone. Shabir Madhi reports financial support was provided by ImmunityBio. Clare L. Cutland reports financial support was provided by BMGF. Clare L. Cutland reports financial support was provided by Pfizer. Clare L. Cutland reports financial support was provided by Biovac. Lee Fairlie reports financial support was provided by South African Medical Research Council. Lee Fairlie reports financial support was provided by Bill and Melinda Gates Foundation. Mookho Malahleha reports financial support was provided by Synergy Biomed Research Institute. Andrew J. Pollard reports financial support was provided by University of Oxford. Andrew J. Pollard reports financial support was provided by Shionogi. Andrew J. Pollard reports financial support was provided by AstraZeneca. Andrew J. Pollard reports financial support was provided by National Institute for Health and Care Research. Qasim Ebrahim Bhorat reports financial support was provided by Wits Health Consortium. Qasim Ebrahim Bhorat reports financial support was provided by Regeneron Pharmaceuticals. Qasim Ebrahim Bhorat reports financial support was provided by GlaxoSmithKline. Qasim Ebrahim Bhorat reports financial support was provided by Avillion. Qasim Ebrahim Bhorat reports financial support was provided by Sanofi. Qasim Ebrahim Bhorat reports financial support was provided by NovoNordisk. Qasim Ebrahim Bhorat reports financial support was provided by Bill & Melinda Gates Foundation. Qasim Ebrahim Bhorat reports financial support was provided by South African Medical Research Council. Qasim Ebrahim Bhorat reports financial support was provided by Novavax. Qasim Ebrahim Bhorat reports financial support was provided by AstraZeneca. Qasim Ebrahim Bhorat reports financial support was provided by Clover BioPharmaceticals. Tonya L. Villafana reports financial support was provided by AstraZeneca. Clare L. Cutland reports a relationship with BMGF that includes: employment and funding grants. Mookho Malahleha reports a relationship with RTI that includes: consulting or advisory. Andrew J. Pollard reports a relationship with UK Joint Committee on Vaccines and Immunization that includes: board membership. Andrew J. Pollard reports a relationship with World Health Organisation SAGE that includes: board membership. Sarah Gilbert reports a relationship with Vaccitech that includes: equity or stocks. Teresa Lambe reports a relationship with Vaccitech that includes: consulting or advisory. Mookho Malahleha reports a relationship with Synergy Biomed Research Institute that includes: board membership, employment, and equity or stocks. Sarah Gilbert has patent issued to Vaccitech. Teresa Lambe has patent issued to Vaccitech.

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Appendix A. Supplementary data

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References

[1] Salyer SJ, Maeda J, Sembuche S, Kebede Y, Tshangela A, Moussif M, et al. The first and second waves of the COVID-19 pandemic in Africa: a cross-sectional study. Lancet 2021;397(10281):1265–75.

[2] Network for Genomic Surveillance South Africa (NGS-SA). SARS-CoV-2 Sequencing Update 12 November 2021. Available at: https://www.nicd.ac.za/wp-content/uploads/2021/11/Update-of-SA-sequencing-data-from-GISAID-12-Nov_Final.pdf. Accessed 22 April 2022.

[3] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397(10269):99–111.

[4] Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet 2021;397(10282):1351–62.

[5] Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, et al. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 vaccine. N Engl J Med 2021;385(25):2348–60.

[6] Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med 2021;384(20):1885–98.

[7] Lu X, Wang L, Sakthivel SK, Whitaker B, Murray J, Kamili S, et al. US CDC real-time reverse transcription PCR panel for detection of severe acute respiratory syndrome coronavirus 2. Emerg Infect Dis 2020;26(8):1654–65.

[8] World Health Organization (WHO). Laboratory testing for coronavirus disease (COVID-19) in suspected human cases: interim guidance, 19 March 2020. Available at: https://apps.who.int/iris/handle/10665/331501. Accessed 22 April 2022.

[9] Quick J. nCoV-2019 sequencing protocol v3 (LoCost) V.3 2020. Available at: https://www.protocols.io/view/ncov-2019-sequencing-protocol-v3-locost-bp2l6n26rgqe/v3. Accessed 22 April 2022.

[10] Pillay S, Giandhari J, Tegally H, Wilkinson E, Chimukangara B, Lessells R, et al. Whole genome sequencing of SARS-CoV-2: Adapting illumina protocols for quick and accurate outbreak Investigation during a pandemic. Genes (Basel) 2020;11(8):949.

[11] Giandhari J, Pillay S, Tegally H, Wilkinson E, Chimukangara B, Lessells R, et al. NEBnext library construction and sequencing for SARS-CoV-2: Adapting COVID-19 ARTIC protocol 2020. Available at: https://www.protocols.io/view/nebnext-library-construction-and-sequencing-for-sa-x54v9m46mg3e/v1. Accessed 22 April 2022.

[12] Addetia A, Lin MJ, Peddu V, Roychoudhury P, Jerome KR, Greninger AL. Sensitive recovery of complete SARS-CoV-2 genomes from clinical samples by use of swift biosciences' SARS-CoV-2 multiplex amplicon sequencing panel. J Clin Microbiol 2020;59(1):e02226–10320.

[13] Cleemput S, Dumon W, Fonseca V, Abdool Karim W, Giovanetti M, Alcantara LC, et al. Genome detective coronavirus typing tool for rapid identification and characterization of novel coronavirus genomes. Bioinformatics 2020;36(11):3552–5.

[14] Minh BQ, Schmidt HA, Chernomor O, Schrempf D, Woodhams MD, von Haeseler A, et al. IQ-TREE 2: new models and efficient methods for phylogenetic inference in the genomic era. Mol Biol Evol 2020;37(5):1530–4.

[15] Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) variant. N Engl J Med 2021;385(7):585–94.

[16] Madhi SA, Kwatra G, Myers JE, Jassat W, Dhar N, Mukendi CK, et al. Population immunity and Covid-19 severity with omicron variant in South Africa. N Engl J Med 2022;386(14):1314–26.

[17] Nasreen S, Chung H, He S, Brown KA, Gubbay JB, Buchan SA, et al. Effectiveness of COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe outcomes with variants of concern in Ontario. Nat Microbiol 2022;7(3):379–85.

[18] Mahase E. COVID-19: What do we know about the delta omicron recombinant variant? BMJ 2022:376o792.

[19] Kirsebom F, Andrews N, Sachdeva R, Stowe J, Ramsay M, Bernal JL. Effectiveness of ChAdOx1-S COVID-19 booster vaccination against the Omicron and Delta variants in England. medXriv 2022;04.29.22274483.